College of Medicine

Evaluating the Impact of Mandatory Folic Acid Fortification Programme on the Prevalence of Spina Bifida in Southern Region of Malawi: A Central Hospital Based Secondary Data Study

By

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Declaration

I, Blessings Chapweteka, declare that this dissertation is my original work and has not been presented for any other awards at the University of Malawi or any other university.

Signature: 

Date: 31st December 2020

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Abstract

Without evidence, we can not know if a Malawian fortification programme of 2015 has been effective. We conducted the study to evaluate the impact of folic acid fortification programme on the prevalence of spina bifida in the southern region of Malawi. We used a pre post case-control quasi experimental comparative study design. We assessed the total number of births for the southern region, Mw in 2014. Then we reviewed case notes of spina bifida patients who presented to QECH from the southern region, Mw in that year (2014). We did the same for 2018. Spina bifida cases were defined as a documented confirmed case note diagnosis of spina bifida, myelomeningocele or meningocele. The control group comprised of case notes of patients who presented to QECH from the southern region with conditions like sepsis, malaria and diarrhea. To obtain prevalence, we divided the number of cases with the total number of births, expressed per 10,000 live births. The prevalence for 2014 and 2018 were compared to assess the programme's impact. We performed logistic regression to assess the odds of spina bifida before and after the programme using; gender, birth weight; tribe; maternal age at delivery; number of children by mother; district of residence; pre-natal use of folic acid and use of chronic medications. The before and after odds were compared to assess for accuracy of prevalence. We used Z test to assess the significance of the odds at 95% confidence interval and 0.05 marginal error. SPSS software version 20 was used. The prevalence increased by 13.6% from the pre-fortification to the post-fortification period. Occurrence of spina bifida was statistically associated with female gender (OR 2.51 (1.019-6.198) p= 0.45), absent history of spina bifida (OR 0.191 (0.41-.884) p=0.034), mean birth weight of 2850g, family size 72% $\leq$3 children and maternal age 77% $\leq$ 30 years. The study showed that the mandatory folic acfortification programme in Malawi might have not been effective in reducing the prevalence of spina bifida.

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Abbreviations and Acroynms

QECH:	Queen Elizabeth Central Hospital
NTD:	Neural Tube Defects
FA:	Folic Acid
MMC:	Mylemeningocele
ZCH:	Zomba Central Hospital
MCH:	Mzuzu Central Hospital
SHIP:	Spina bifida and Hydrocephalus Interdiscplinary Programme
USA:	United States of America
LIC:	Lower Income Countries
WHO:	World Health Organization
CO:	Carbon Dioxide
NO2:	Nitrogen Dioxide
M&E:	Monitoring and Evaluation
Mw:	Malawi

Chapter One: Introduction

1.1 Background

Since the introduction of mandatatory folic acid food fortification programme in Malawi in the year 2015, no research has been done to evaluate its impact on spina bifida prevalence [1]. Without a specific scientific evaluation, once a fortification programme has been initiated, it is difficult to know whether it is on course or not, or whether subsequent improvements in occurrence of neural tube defects like spina bifida in a population are due to the fortification programme or to other changes, such as, improvements in socio-economic status or in public health provision, that occurred over the same period of time [2]. One method of evaluating a folic acid fortification programme in many countries where it is in use, has been a comparison of spina bifida prevalence prior to and after the programme [2]. In Malawi like many other African countries, there is paucity of documented data on spina bifida prevalence. There have been efforts to document the prevalence. Msamati and others in 2000, conducted a hospital based study at Queen Elizabeth Central Hospital (QECH) in Blantyre where they established that spina bifida had an incidence of 0.47/1000 [3]. The current study did not use that incidence because it is on the lower side as compared to the incidence range of 1 to 11/1000 births which has been documented for several developing countries with similar social economic status like Malawi [4]. It is even lower than a prevalence of 1.87 to 8.9 per 1,000 reported in Malaysia, a country with better social economic indicators than Malawi between 2003 and 2016 [4]. Furthermore the methold used to establish that incidence is different from this study. Additionally, the incidence was established some 15 years before the fortification programme and many factors might have changed to affect its relevance in the current study.

Although there is documented incidence of spina bifida prior to the inception of folic acid fortification programme in Malawi, there is none documented after the programme became operational in 2015. That way it is difficult to assess the impact the programme has made. That is why the investigator wanted to establish the pre and post fortification prevalence inorder to assess the impact of the mandatory folic acid food fortification programme.

1.2 Introduction

Neural tube defects (NTDs) are the second most common group of serious birth defects globally [5]. NTD comprises of three conditions namely spina bifida, anencephaly and encephalocele, spina bifida is the commonest of all [6]. Each year, 300,000 to 400,000 infants worldwide are born with spina bifida and anencephaly, of which around 200,000 are spina bifida [5]. Globally, the prevalence of spina bifida is documented within a range of 0.5-11 per 1,000 live births, particularly in developing countries like Malawi [4, 7]. In Malawi, Msamati in 2000 reported that spina bifida had an incidence of 0.47/1,000 live births.

Spina bifida is a congenital birth defect in which the vertebral column is open, often with spinal cord involvement [8]. It occurs within the first 28 days after conception, and therefore occurs before most women are aware of their pregnancy [9]. Clinically most significant is myelomeningocele type of spina bifida in which the spinal neural tube fails to close during embryonic development [10]. The exposed neural tissue degenerates in utero, resulting in neurological deficit that varies with level of the lesion [10]. Spina bifida reduces the quality of life greatly. Patients with the condition presents with varying degrees of paralysis, motor impairment, developmental delay, lack of sensation that enhances the risk of pressure sores, urinary and fecal incontinence, renal failure, orthopedic abnormalities including; club foot, contractures, hip dislocation, scoliosis and kyphosis [8]. Hydrocephalus is also a common complication of spina bifida [11] . These problems cause significant burden to the patients and their families [5]. In addition to the physical problems, persons with spina bifida face significant psychosocial problems. A Kenyan study found that persons with spina bifida and their families are likely to present with emotional distress due to lack of acceptance from their communities [5]

[6]. Treatment for spina bifida includes surgery, medication, and physiotherapy. Regular monitoring and ongoing therapy are often necessary to prevent and manage complications throughout the individual's life [5].

Locally patients with spina bifida are managed at Queen Elizabeth Central Hospital (QECH) in southern region, Zomba Central Hospital (ZCH) in southern eastern region, Kamuzu Central Hospital (KCH) in the central region and recently Mzuzu Central Hospital (MCH) in northern region. QECH manages most of the patients, it is situated in Blantyre district and although a central hospital, it serves as a district hospital due to absence of one in the district. Every spina bifida patient presenting at a hospital facility other than those central hospitals, will be referred accordingly. In the southern region, the patients are mainly managed at QECH where a programme called Spina Bifida and Hydrocephalus Interdisciplinary Program (SHIP) specifically set up to provide leadership in the management of spina bifida at QECH and Malawi is based and currently headed by the investigator. QECH has a bed capacity of around 1,200 with one fifth comprising of the paediatrics department.

Occurrence of spina bifida has been associated with certain factors. These include, pre-natal use of folic acid supplementation, child's gender, maternal child bearing age, birth weight, ethnicity, prenatal use of chronic medication, family history of spina bifida and genetics [12–14].

Just like with many other conditions, there have been efforts to control this condition. Spina bifida is preventable in up to 50% of the cases by adequate intake of folic acid supplementation by women of the reproductive age prior to pregnancy and during the first 3 months of pregnancy

[15]. Folic acid can be added to staple foods to achieve the same purpose and this is known as fortification where folate is synthetically added to a food vehicle, commonly maize and wheat flour [1, 16]. This study is interested in the fortication programme in Malawi where legislation for mandatory folic acid fortification using flour and wheat was passed in parliament in 2015 with an aim of reducing the occurrence of neural tube defects like spina bifida [1].

1.3 Objectives of the Study

1.3.1 Broad Objective

The overall aim of this study is to evaluate the impact of folic acid fortification programme on the prevalence of spina bifida in the southern region of Malawi.

1.3.2 Specific Objectives

1) To establish the prevalence of spina bifida in southern region of Malawi for 2014 and 2018.
2) To understand the pattern of geographical distribution of spina bifida cases in southern region of Malawi.
3) To establish risk factors associated with spina bifida in the southern region of Malawi.
4) To establish between period differences and risk factors associated with spina bifida in Malawi

1.4 Research Justification

Studies have proven that the medical costs for patients born with spina bifida are very high at lifetime cost of $600,000 (approximately 462,000,000 Malawi Kwacha) in the USA [8]. In Malawi the lifetime cost is not documented and it cannot be as high as that of the USA taking into account differences in health systems requirements, economy size and citizens' earning power. However, the lifetime cost for USA gives a hint that even in Malawi, spina bifida poses a significant economic burden to the government, families and the persons with the condition [15]. Many studies have concluded that governments would save a lot of money by utilizing an effective fortification programme to reduce the occurrence of spina bifida [8, 10]. As such it is imperative in a poor country like Malawi to ascertain whether such a programme is achieving the intended purpose or not, otherwise it would remain a drain of resources. Therefore an effort to evaluate the efficacy of the folic acid fortification programme is important. Evidence will provide important information for policy and enforcement of strategy that could lead to a reduction in risk of spina bifida [10].

Chapter Two: Literature Review

Spina bifida has a long established documented scientific history extending back to Ancient Egyptian times: fetuses and infants with spina bifida were reported in ancient Egyptian times [5]. Although prevalence data is readily available in developed countries, it is limited in lower income countries (LIC) like Malawi [17]. According to WHO some reasons for the limitations are constrained diagnostic capability, poor health related statistics, lack of birth defect surveillance and registries and reliance on hospital-based rather than population-based studies [18]. To improve the situation WHO passed a resolution on birth defect surveillance [17].

Unlike the developed countries, the prevalence of spina bifida remains high in the developing countries at the the prevalence of 0.5 to 11 per 1,000 live births. In Malaysia, spina bifida prevalence is documented within a range of 1.87 to 8.9 per 1,000 live births [4]. In sub-Saharan Africa, it is known that there are an estimated 37,000 children born with spina bifida every year [17]. In Malawi, Msamati and collegues in their study at QECH established that spina bifida had an incidence of 0.47/1000 in 2000 [3]. This incidence contradicts the reported incidence of 0.5 to 11 per 1,000 live births for countries with poor social economic status similar to Malawi. The lower incidence reported in Malawi could be due to a hospital based study conducted. It is anticipated that this study might face a similar limitation and the investigator has justified why it is worthwhile to conduct the study.

It is worthy noting that the incidence and prevalence of spina bifida varies when pregnancy losses are taken into account. Up to 20% of fetuses with spina bifida die *in utero* as stillbirths or as therapeutic abortions [19]. This could imply that studies that report incidence/prevalence from live births only could be under-estmating the incidence/prevalence. It is however anticipated that this study will face the same limitation as it is considering patients that survived and were referred to QECH for treatment. It is still worthwhile to conduct the study because it will be the first documented of this kind from which subsequent studies can build on. Secondly the prevalence obtained would hint as to what extent still births/pregnancy losses could be impacting on the true prevalence and that finding is revealing to stimulate further research. For example a lower than internatonally accepted prevalence for the region, should hint that they are many cases that are not making it to the referral hospital and still births/pregnancy losses could be a possible explanation. That would be a finding worth of stimulating further research in the future. Thirdly, it is worthwhile to proceed with the study from hospital records because the study will use a similar approach to establish the prevalence for both 2014 and 2018, therefore incase the prevalence is not valid, it will still be reliable to assess the impact of the programme. Lastly, it is worthy mentioning that spina bifida being a congenital defect (present at birth), the hospital accords favourable place to identify it. This is the case because the majority of births at 91% are occurring at the hospital setting [20]. This further justifies why a hospital based study is applicable.

The development of spina bifida has been associated with certain factors. These factors incluede pre-natal use of folic acid supplementation, child's gender, maternal child bearing age, birth weight, ethnicity, prenatal use of chronic medication, family history of spina bifida, genetic and environmental factors such as air pollution and chemical exposure [12–14].

Folic acid supplementation has been proven to reduce the occurrence of spina bifida by 50%-70% [21, 22]. In a study done in 2010 by Lopez-Camelo and others, found that folic acid fortification was associated with a decrease in the proportion of spina bifida cases [15]. Bell and Oakley, using the March of Dimes estimates, calculated that of the more than 300,000 NTD-affected pregnancies worldwide yearly, the majority (more than 200,000) are probably preventable with folic acid supplementation [9]. It is widely recognized that adequate consumption of folic acid before pregnancy and during the early weeks of gestation protects fetuses from developing neural tube defects (NTDs) inclueding spina bifida [9]. Further studies show that low levels of folate in pregnancy predisposes women to giving birth to a child with spina bifida [7]. The normal levels of serum folate (folic acid) in adults are 2-20 μg/L, or 4.5-45.3 nmol/L, while in Red Blood Cells it is 140-628 μg/L or 317-1422 nmol/L. Biochemical deficiency has been defined as a concentration of less than 3 μg/L (< 6.7 nmol/L) for serum folate and less than 140 μg/L (< 322 nmol/L) for erythrocyte folate [23]. The researcher was not able to establish how many female adults of child bearing age are folic acid deficiency in Malawi, however it is belived that a significant number of them would be deficient considering that the diet is poor and that we have a culture of overccoking food like green leafy vegetables which contains folic acid and that practice destroys the folic acid which is heat sensitive [14].The demand for folate increases during pregnancy[23]. Inorder to reduce the risk for the development of neural tube defects like spina bifida, many governments in the world have programmes for folic acid supplements in pregnancy or folic acid fortification. Folic acid supplements may only provide part of the answer to occurrence of spina bifida; child's gender, maternal age on delivery, birth weight, ethnicity has been implicated among others.

As regards to gender, there is contradictory evidence as to which gender is at most risk of spina bifida. In South America, the rates of NTDs inclueding spina bifida were around 18/10,000 births for females and 12/10,000 births for males [24]. Others authors suggest that males are at a greater risk [12] . The researcher sides with the finding that females are at a greater risk and he approve of the finding that folic acid fortification could be playing a role in the contradiction [7]. Folic acid may have an increased protective effect on females than males [7]. This means that in countries where fortification has been implemented, the population of male persons with spina bifida could be more than females due to folic acid averting more female spina bifida cases than males. This has been affirmed by comparing the female and male spina rates before fortification and after fortification. For example, in South America, a study conducted before fortification was implemented showed that the rates of NTDs including spina bifida were around 18/10,000 births for females and 12/10,000 births for males [24], while a study conducted after fortification was implemented in Malaysia showed that males constituted more than half of the overall cases of spina bifida at 59% [7]**.**

Maternal age at childbirth is another risk factor. Women giving birth at age below 35 years old are at greater risk of giving birth to children with spina bifida [7]. Another factor is birth weight. Low birth weight has been suggested as risk factor for spina bifida [7]. According to the Center for Disease Control (CDC), newborns should weigh more than 2.5 kg [7]. This implies that babies born with birth weight lower than that might be at an increased risk of spina bifida**.** Ethnicity has also been found to be associated with spina bifida [17, 25]. There are other factors associoated with occurrence of spina bifida like maternal use of chronic medication and exposure to pollutants.

Pre-natal use of medicines like valproic acid exposes mothers to giving birth to a child with spina bifida. Valproic acid, a widely used anticonvulsant, has shown to increase the risk of NTDs, spina bifida included by approximately 10-fold when taken early in pregnancy [19].

The family social status is another risk factor for the development of spina bifida. Many studies have concluded that NTDs are more prevalent among women in lower social strata [9]. In low income setting with low educational attainment and poor socioeconomic status like Malawi, the true incidence of spina bifida should be higher than in high income countries [17]. Environmental factors like air pollution and chemical exposure also play a role in the development of spina bifida [10]. Although there have been some contradictions on their significance, several studies do find increased risk associations between early prenatal exposure to air pollution and neural tube defects [26]. Pandula and others in their 2013 study found an association between carbon monoxide (CO) and nitrogen dioxide (NO2) and increased risk of spina bifida [26]. It is thought that spina bifida being a structural birth defect could be caused by a complex combination of genetic and environmental factors that interact to interfere with morphogenetic processes [26]. However, in the Malawian context, air pollution and chemical exposure could not be playing a significant role in the occurrence of spina bifida. This should be the case because many spina bifida cases originates from the rural set up where air pollution from carbon monoxide and nitrogen dioxide is very much minimal due to the absence of vehicles and industries [27]. The researcher is cognizant that women in rural areas might be exposed from carbon monoxide pollution from open air cooking using firewood. However it is suggested that the pollution is not significant as compared to that originating from vehicles and industries.

It is worth noting that even though folic acid has proven to reduce the risk of spina bifida, not all pregnant women will be protected. Indeed, folic acid deficiency is a risk factors for spina bifida, however, in many studies, maternal folate levels in some affected pregnancies are within the normal range, arguing against a simple folate-deficiency model [28]. This implies that genetics could also be playing a role in the occurrence of spina bifida [10].

The genetic component of spina bifida has been estimated at 60-70% [10]. Evidence for genetic causation includes the high recurrence risk for siblings of index cases which is approximately 50-fold more than in the general population, together with a gradually decreasing risk in more distant relatives [10] . Women with two or more affected pregnancies have a very high risk of approximately 10% of further recurrence [10]. Adding to the genetic predisposition, a study showed that NTD including spina bifida prevalence is greater in like-sex twins (which are assumed to include all monozygotic cases) compared with unlike-sex pairs [10]. It is accepted, therefore, that genetic factors contribute importantly to NTD/spina bifida risk, although the precise nature of this genetic contribution remains unclear [19]. The genetic revelation has lead researchers to conclude that only 50% of NTD including spina bifida could be prevented with folic acid. There has not been general consensus on the folic acid preventable spina bifida as some have estimated it to be at 70%. In Malawi the majority of persons with spina bifida comes from a poor background with poor access to nutrition [27]. Therefore the investigator holds the view that the Malawi case could be that folate deficiency plays a greater role in the development of spina bifida than genetics, because had it been that genetics has a major role; we could have been seeing a balance in the cases across socio-economic statuses. This gives hope that an effective folic acid programme could play a significant role. Folic acid supplementation has never gone without counter arguments.

Others have argued that folic acid's preventive effect could be misleading as the impact could be due to what they termed as terathanasia implying the disappearance of NTD due to folic acid induced early pregnancy loss. In their counter argument, Copp (2014) and his colleagues mentioned that there was indeed a small excess of miscarriages in the folate-treated group of the their trial, and that finding was interpreted as folic acid encouraging survival of some pregnancies to a stage when their loss could be recognized (as miscarriage) [28], implying that even without folic acid supplement, the miscarriages would happen anyway, just earier. To some extent the lower than normally internationally acceptable documented incidence of 0.47/1,000 by Msamati in Malawi could partly be attributed to this reason where other cases were missed due to pregnancy loss. In Malawian setting, it is opionated that it might be difficult to count pregnancy related spina bifida losses because of the culture of secrecy surrounding pregnancy and due to the fact that most of these losses could be happening at home other than the hospital since many woman have not yet started ante natal visits by the time the loss occur [20]. This research will therefore face the same limitation of not taking into account pregnancy related losses. The researcher lacked adequate resources and time to take that into account and it has been justified earier why it is still valuable to conduct the research.

Even though it has been shown that spina bifida might be associated with a number of causative agents other than folic acid deficiency, so many studies have singled out folic acid as the major contributor to spina bifida and folic acid fortification has been recommended as control measure [9].

Folic acid fortification is the deliberate synthetic addition of folic acid in staple foods, so as to increase the intake in order to prevent NTD like spina bifida [25]. A fortification programme can target everyone by fortifying foods that are widely consumed by the general population (mass fortification) as in the Malawian case which uses maize and wheat flour as food vehicles [2]. Fortification can also be designed for specific population subgroups, such as complementary foods for young children or rations for displaced populations (targeted fortification). Fortification can also be tailored to allow food manufacturers to voluntarily fortify foods available in the market place (market-driven fortification) [2] . Mass fortification is nearly always mandatory as is the case in Malawi. Targeted fortification can either be mandatory or voluntary. Market-driven fortification is always voluntary, but governed by regulatory limits [2]. The choice between mandatory or voluntary food fortification usually depends on national circumstances [2]. Many countries are implementing fortification programmes to achieve that purpose. For example by 2009, 51 countries had regulations written for mandatory wheat flour fortification programmes that included folic acid [9]. As of now over 80 countries have adopted folic acid fortification as a policy, either mandatory (in which case is Malawi) or voluntary. The effectiveness of folic acid fortification of staple foods in the prevention of neural tube defects has been well documented in the United States, Canada, Costa Rica and Chile, where folic acid fortification of staples has been implemented since 1998 and 2000. The Australian government has also recently introduced mandatory folic acid fortification of bread [29]. In Asia and Europe fortification is not common. In Africa, South Africa was the first country to adopt mandatory folic acid fortification of staples in 2003, and a 30% decline in the prevalence of neural tube defects has been observed from pre-fortification to post-fortification [20]. In 2012, the Kenyan Ministry of Health mandated folic acid fortification in maize and wheat flour [28]. Burkina Faso and Morocco are also implementing mandatory fortification of folic acid using maize and wheat flour [22]. Malawi followed other countries to adopt the program in 2015 for maize and wheat flour [1].

A higher prevalence of spina bifida was seen in countries without mandatory folic acid fortification programmes[22]. Prevalence estimates of live births spina bifida from 1985 to 2010 were lower in regions with mandatory fortification policies [21]. Eliminating the suspicion of mandatory folic acid fortification effectiveness, one study showed that even when still births and terminations of pregnancy were not taken into account, It still showed that mandatory fortification was effective in lowering the prevalence of spina bifida [22].

Apart from the mandatory fortification programme, there have been other strategies that have been implemented to control NTD. Folic acid tablet supplementation for example. Research shows that they have failed [22]. Despite the WHO peri-conceptional folic acid tablet supplementation recommendations, studies show that many women still do not follow the recommendations, particularly women of low socioeconomic status like Malawi. This is also true in one study; though 17% of the participants had preconception care, only 7.8% took tablet supplements [17]. Fortification has shown to be superior to tablet supplementation. One study showed that public health messaging aimed at increasing folate supplement consumption has not had the same effect as mandatory folic acid fortification on increasing serum folate levels and reducing the birth prevalence of neural tube defects [22]. In Malawi folic acid tablet supplementation for this purpose is not practiced, however SHIP as a programme provides tablet supplements to mothers that have children with spina bifida and adolescent young girls with spina bifida. This is done in view that they are at an increased risk of giving birth to another child with spina bifida. Other strategies for supplementation include incorporation of folate within an oral contraceptive [28]. Little research is published on the same. However, it is believed that its efficacy could be less superior than fortification especially in Malawi. This can be the case because contraceptive uptake in particular by rural women who would be the target group in this case, is low according to the contraceptive uptake report in Malawi[30]. Strong scientific evidence has concluded that mandatory fortification is often more efficacious and cost-effective than the other strategies, especially if an appropriate food distribution system is in place [31]. Fortification programmes globally, has not achieved the same impact [9, 21]. This indicates that there is more to just a policy in as far as achieving the intended purpose is concerned. Therefore the investigator was interested to find the determinants of an effective folic acid fortification policy.

It is documented that effective programmatic strategies of mandatory folic acid fortification will incorporate systematic consideration of sound programme management, ensure consumption of fortified foods, and promote advocacy and supportive legislation [32]. This entails that an effective mandatory fortification policy is more than just passing a legislation. There have to be additional deliberate strategies to ensure that the fortified products reach the intended target. This could not have been the case in Malawi. For example, fortified maize or wheat flour can only be accessed in urban shops which are inaccessible by the majority of rural women who would benefit. Fortified foods often fail to reach the poorest segments of the general population who are at the greatest risk of the deficiency [31]. This is because such groups often have restricted access to fortified foods due to low purchasing power and an underdeveloped distribution channel of the fortified product[31]. Many women who would benefit from the fortified flour often live on the margins of the market economy, relying on own-grown or locally produced food [31]. In populations who rely on these staples, it may be difficult to find an appropriate food to fortify such is the case in Malawi where most Malawians rely on milled flour [31]. The researcher made attempts to establish the tonnage of fortified flour for maize and wheat available and sold into the Malawian market between urban and rural set up to no avail. It is believed that the statistics would hint on accessibility of folic acid fortificant between the rural and urban areas and inturn aid in explaining the difference in prevalence between the two. Even though this data was not available, it is known that very little fortified flour for both wheat and maize would be reaching the rural area. That should partly explain why the rural areas would be producing more cases of spina bifida.

To ensure an even distribution and access of folic acid fortificant with maize flour, It is recommended in poor countries, Malawi likewise where there is high reliance of small mills to resort to utilization of the mills as fortification points [33]. Some quarters have the opinion that enforcement of mandatory fortification might be impractical in this scenario and have suggested that under such circumstances, small mills should be allowed to fortify their product (flour) on a voluntary basis but following specified regulations [31]. The researcher agrees with utilization of smalls mills but does not agree that it has to be voluntary because as shown ; voluntary fortification has a number of gaps.

Technological issues relating to food fortification also determines the program's effectiveness. There is need to ensure that the technology used for fortification does not affect the food's acceptability by consumers including taste [31]. For example, some folate fortificants change the colour and flavour of many foods to which they are added [31]. The researcher opionates that in Malawi, sugar, which is widely accessible, would have been ideal agent for folic acid fortification, however it changes color with folate fortificant and affects acceptability by the buyer and hence producers are not willing to implement that fortification at the expense of losing customers [2].

Accessibility to a fortified food vehicle do significantly affect the effectivess of the programme. Countries whose programmes have failed, might have given less attention to the accessibility of the fortified food vehicle by the beneficiary. To demonstrate the complexity of this issue; despite having access to the same epidemiological evidence, countries like the United States, Australia, Ireland had adopted mandatory folic acid fortification while the United Kingdom and Finland had not [2]. It is reported that it has been partly due to decisions as regards to which food vehicles can been selected and what level of folic acid fortification could be implemented [2]. So yes it is beyond just having a fortication programme. Rather than a case of one size (mandatory folic acid fortification programme) fits all (national circumstances), the programme should be determined on a country-by-country basis [2]. As a general rule, the more widely and regularly a fortified food is consumed, the greater the proportion of the population likely to benefit from food fortification [31].

Adding to the prerequisites for an effective flour fortification programme, World Health Organization (WHO) mentions that designing and implementing an effective monitoring and evaluation (M&E) system is an integral element of wheat and maize flour fortification programs [34]. WHO M&E framework for food fortification programmes identifies two components of food fortification programmes that require different assessment approaches: 1) food control and regulatory monitoring to assess the supply of adequately fortified foods (nationally produced or imported), and 2) program-based M&E to track the population's access to and use of fortified foods and the impact of the intervention on the health and nutrition of the population [34]. It is not clear whether the WHO guidelines are implemented in Malawi.There is still more to an effective fortification programme.

Some have argued that the global tendency towards urbanization means that an ever increasing proportion of the population, including that in developing countries is consuming industry-processed, rather than locally-produced foods and that this affords many countries the opportunity to develop effective fortification strategies of staple foods to combat NTD like spina bifida [31]. This is not the case in Malawi where urban migration does not necessarily mean access to decent life. There are a number of peri urban areas which have been categorized as urban like Ndirande, Zingwawa, Bangwe among many others, whose dwellers continue to utilize flour directly from the mill other than shops like Chipiku, Peoples Trading Centre or Spars which stock fortified flour.

Mandatory fortification might have limitations. For example, a specific fortified foodstuff might not be consumed by all members of a target population. Conversely, everyone in the population is exposed to increased levels of micronutrients in food, irrespective of whether or not they will benefit from fortification [31]. Periodic measurement of the population folate levels might help to inform policy amendment.

Chapter Three: Methodology

3.1 Study Design

The current study used pre-post case control quasi experimental comparative study design. From February, 2020 to August, 2020, we assessed the number of total births that occurred in the southern region of Malawi in 2014, one year before the mandatory folic acid food fortification programme became operational. Thereafter we reviewed case notes of spina bifida patients who presented to QECH from the southern region in that year (2014). We did the same for 2018, three years later into the program. Spina bifida cases were defined as a documented confirmed case note diagnosis of spina bifida, myelomeningocele or meningocele [6] .

We also reviewed case notes of patients who presented to QECH with diagnoses other than spina bifida. These patients who also came from the southern region of Malawi, had conditions like sepsis, malaria and diarrhea. These formed a control group.

The study design was suitable because it facilitated comparision of the prevalence before and after an intervention of mandatory folic acid food fortification programme. It also enabled the researcher to assess and compare risk factors for the condition before and after the programme and determine if they had an influence on the prevalence.

3.2 Study Setting

The study was conducted in the southern region of Malawi where the population came from. Participants' case notes were accessed at Queen Elizabeth Central Hospital (QECH), paediatric department. QECH is a major referral hospital situated in Blantyre, southern region, Malawi, subSahara region. It is a referral hospital for all the 13 districts of the southern region of Malawi which had a population of 7,750,629 or 44 percent of Malawi population at the time of the study [35, 36]. It is estimated that the region registered 231 607 births in 2014 [35, 37]. In the absence of Population and Housing census in that year (2014), the number of births has been estimated by considering that children who were 4 years in the recent Malawi Population and Housing Census (MPHC) of 2018 were born in 2014. It was further considered that some children born in 2014 might have died before the recent MPHC and the number of deaths was estimated at 6.7 deaths per 1000 and that have been added to estimate the total number of births. In 2018 there were 237,386 births in the southern region of Malawi according to the recent MPHC [36, 38].

The setting was applicable because it is known that the majority of spina bifida cases from the southern region present to this hospital for treatment. This being the case because QECH is designed to serve patients for the region. Furthermore, QECH in additional to being a central hospital, it functions as a district hospital for the district of Blantyre due to the absence of one in the district. Simillary unlike in the past, a maojority of births are occurring in hospital setting, estimated at 91% [20].

3.3 Study Population

The population for the study was all births in 2014 and 2018 respectively from the southern region of Malawi.

3.3.1 Inclusion Criteria

The study included all case notes of persons with spina bifida diagnosis of either sex and of age equal to or less than 12 months who presented or were referred to QECH from the southern region of Malawi in 2014 and 2018 born in those years.

For the control group we included case notes of persons without spina bifida or other congenital diagnosis of either sex and of age equal to or less than 12 months. Their diagnoses included malaria, sepsis and diarrhea.These also came from the southern region of Malawi in 2014 and 2018 born in the same year.

3.3.2 Exclusion Criteria

For the case group, we excluded all case notes with a confirmed diagnosis of spina bifida whose records were not complete to extract meaningful data. Cases notes of patients that presented to the facility in years other than 2014 and 2018 were also left out. Simillary case notes of spina bifida patients that were born outside the years of 2014 and 2018 were not included. Lastly spina bifida patient case notes that presented to the facility from other regions other than the southern region, Mw were left out.

For the control group, all case notes with a diagnosis of spina bifida or any other congenital condition were excluded. Cases notes of patients that presented to the facility in years other than 2014 and 2018 were also left out. Simillary case notes of patients that were born outside the years of 2014 and 2018 were not included. Lastly case notes that presented to the facility from other regions other than the southern region, Mw were left out.

3.4 Sample Size and Justification

Gedefaw and colleagues established a prevalence for spina bifida of 51 per 10,000 in Ethiopia [17]. At the prevalence of 0.0051% this is a very rare condition such that the standard sample calculation yields an impractical sample of 1 [39]. As such the researcher thought of other methods. Utilizing a modified formula for calculating the prevalence at a confidence level of 95% and a marginal error of 5% [39–42], the sample size is found to be 152. However, in this study the cases are already known, hence the investigator has adopted a sampling technique which Omer and colleagues used in Khartoum, Sudan when they conducted almost a similar study on prevalence of Neural Tube Defects (NTD). In that study they used what they called "Total coverage" sampling method where they included all patients with the condition of interest presenting to the study area within the years of interest [15]. This study included as sample all the cases of spina bifida that presented to QECH from the southern region of Malawi within the years of interest of 2014 and 2018 born in that year. The years of 2014 and 2018 were arrived at in order; to compare the prevalence before and after mandatory folic acid legislation which was passed in 2015 [1]; secondly because latest reliable number of births are only available for 2018 from the Malawi National Statistical office [35]. According to the Spina bifida and Hydrocephalus Interdisciplinary Program (SHIP) database there were 42 cases of spina bifida that presented to QECH in 2014 and 49 cases in 2018 (total of 91) that were from the southern region of Malawi [27]. These formed the sample for the case group.

Of the 91 records that were identified as spina bifida case referrals from the southern region, 14 case notes were missing from the archive; five (5) for 2014 and nine (9) for 2018. This meant that of the 91 patients that presented to QECH in 2014 and 2018, seventy seven (77) case notes were available from the archive, 37 for 2014 and 40 for 2018.

To obtain the sample for the control group, we utilized a ratio of 1:1 thus for 2014 we identified 37 case notes. Simillary 40 case notes were identified for 2018. The control group comprised of diagnosis of malaria, sepsis and diarrhea.

The researcher is cautious that there might be a significant number of spina bifida cases from the southern region that did not present to QECH because they died or they were born at home. The sample is still justifiable because MDHS has shown that a majority of 91 % births are occurring in hospital setting with a minority of 7% occurring at home [20]. We are furthermore more justifiable because mortality of spina bifida has been recorded at 6.9%, this may indicate that a majority survived to the referral hospital at QECH[43]. The study will therefore yield a statistical power of 80% with a significance level of 95% at 0.05 marginal error [42].

3.5 Selection of Study Participants

The study utilized purposive sampling of all the case notes of patients with spina bifida that presented to QECH from the southern region in the years 2014 and 2018. Similary case notes of patients with any diagnoses other than spina bifida or other birth defect were selected using the same criteria for the control group.

3.6 Data Collection Methods and Tools

The study used de-identified patients case notes from which data was retrieved manually and thereafter entered by a data clerk into a proforma (see appendix 1).

3.7 Data Collection Process

Permission was sought from the hospital director and relevant departmental heads before commencing data collection. The de-identified case notes were identified through admission registers, surgical patients' database and SHIP records. The case notes were thereafter retrieved from archive i.e. clerk office and Health Management Information System (HMIS). Two data ward clerks were responsible for retrieving the case notes. They were oriented on how to identify spina bifida case notes. They were specifically oriented on different terms and abbreviations used to describe the condition in the case notes. Thereafter a research assistant collected variables of interest from the case notes such as; patients' gender, birth weight; maternal age at delivery, tribe, use of chronic medications, prenatal use of folic acid and history of pre natal folic acid supplementation [7, 10, 26, 42, 44].

3.8 Data Management

Case notes were only accessed by those directly related to the study. The case notes were anonymized before access by persons assisting with the study who are not involved in direct care of these patients. Data was extracted from patients' case notes into hard copy proforma without patient name, instead identification codes were used e.g. 001/14/ for the cases 2014 or 002/14 for the controls 2014. Both the case notes and proforma were stored in the investigator's office within the premises of QECH to which access is only upon his permission. Thereafter data was entered in a private password protected computer. Data was crosschecked at all levels of entry by a second person.

3.9 Data Analysis

Data was analyzed using SPSS version 20. To estimate the prevalence, yearly spina bifida cases (numerator) that presented at QECH from southern region was compared to yearly number of births (denominator) from the southern region, Mw for both 2014 and 2018. This was expressed per 10,000 live births [4, 6].

A logistic regression analysis was perfomed for the cases and controls for both 2014 and 2018 to obtain the odds ratio. Z test was used to determine the significance of the odds ratio at 95% confidence interval (CIs) before and after the programme. The following risk factors were assessed; gender; birth weight; maternal age at delivery; tribe; prenatal use of folic acid tablet supplementation, prenatal use of chronic medications, and district of origin [7, 10, 26, 42, 44]. The odds ratio for 2014 were compared for 2018 to ascertain if they had an influence on the post fortification (2018) prevalence outcome.

Chapter Four: Results

Through February to August 2020, the investigator assessed 91 records of spina bifida cases from SHIP records being referrals to QECH from the southern region, Malawi.These formed the case group. For the same period, 77 case notes of diagnosis comprising malaria, sepsis and diarrhoea were reviewed and these formed the control group.

Amongst the cases, 42 came from the southern region in 2014, a year that registered 231,607 births representing a prevalence of 1.81. In 2018, 49 cases also came from the southern region of Malawi, in which year there were 237,386 births representing a prevalence of 2.06 as shown in table 1.

Table 1: Spina bifida prevalence for southern region, Mw

	2014	**2018**
Number of cases	42	49
Number of births	231,607	237,386
Prevalence (per 10,000)	**1.81**	**2.06**

The prevalence increased by 13.8% from 2014 to 2018.

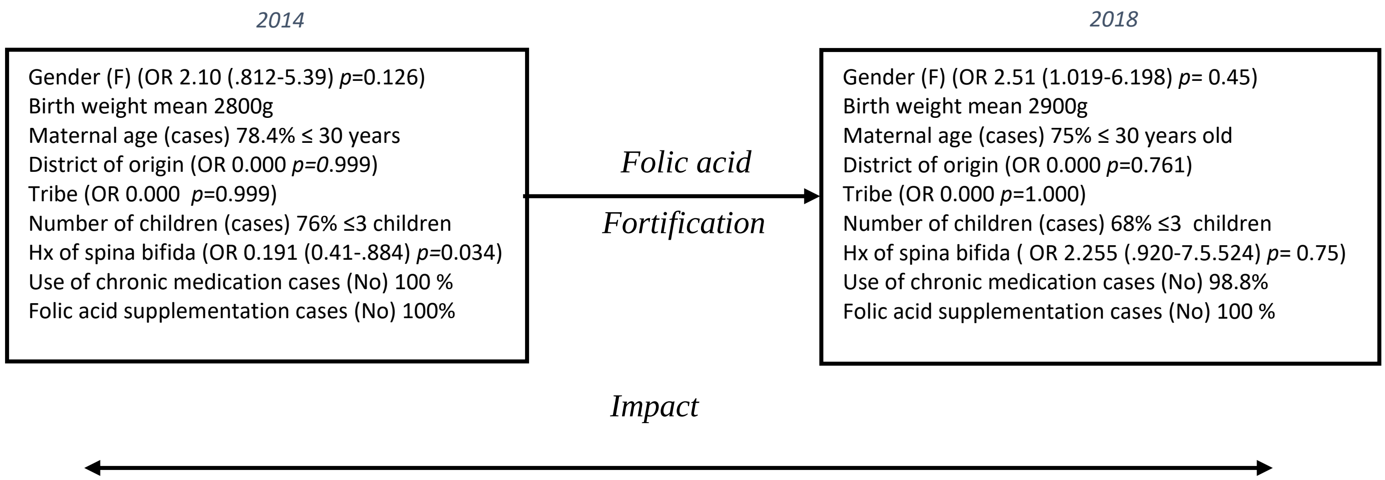

Figure 1: Comparison of statistics in time difference

Spina bifida was associated with female gender for both 2014 and 2018. The mean birth was almost similar between the years. A majority of women who had a child with spina bifida were less than or equal 30 years both 2014 and 2018. Spina bifida occurrence was not associated with the district of origin. Simillary tribe was not associated with spina bifida. It is shown that spina bifida was more likely to occur in a family size of less than or equal to three children. In 2014 negative history of spina bifida was significantly not associated with occurrence of spina bifida while in 2018 it was non significantly associated with negative history of spina bifida. A majority of mothers in the case group had neither used a chronic medication or folic acid tablet supplementation in all the years.

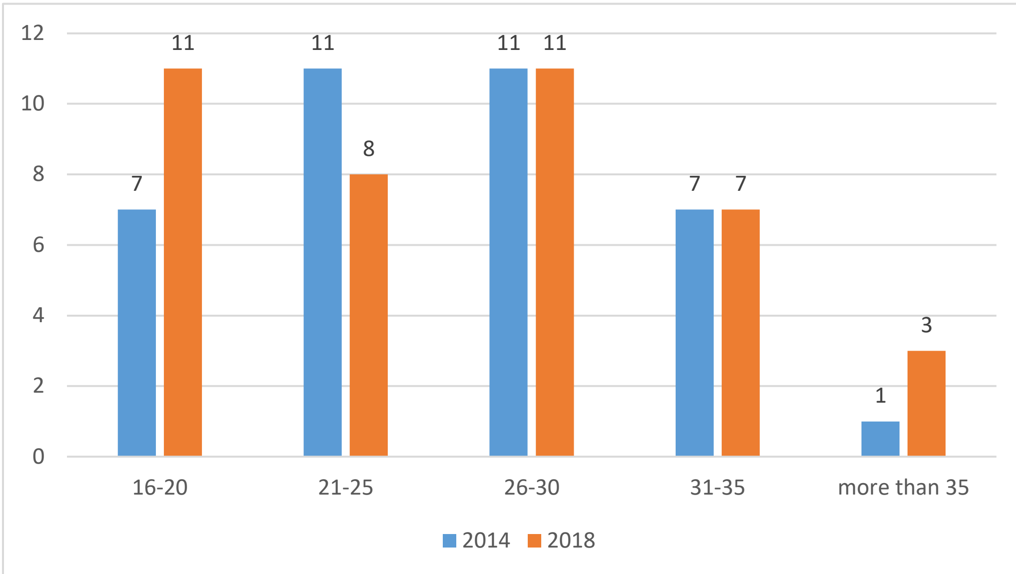

Figure 2: Maternal age on delivery for the cases

In 2014, 78 % of mothers who had children with spina bifida had given birth at 30 years or below while in 2018, 75% had given birth at that age.

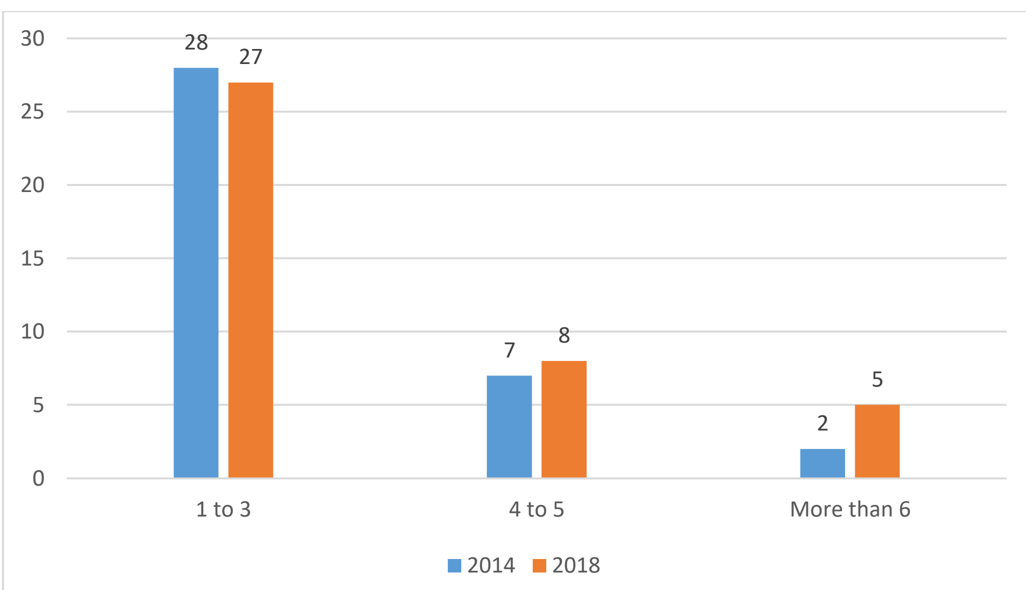

Figure 3: Number of children by mother

In 2014, 76% of mothers with a spina bifida child had a family size of ≤3 children while In 2018, 68 % had a family size of ≤3 children

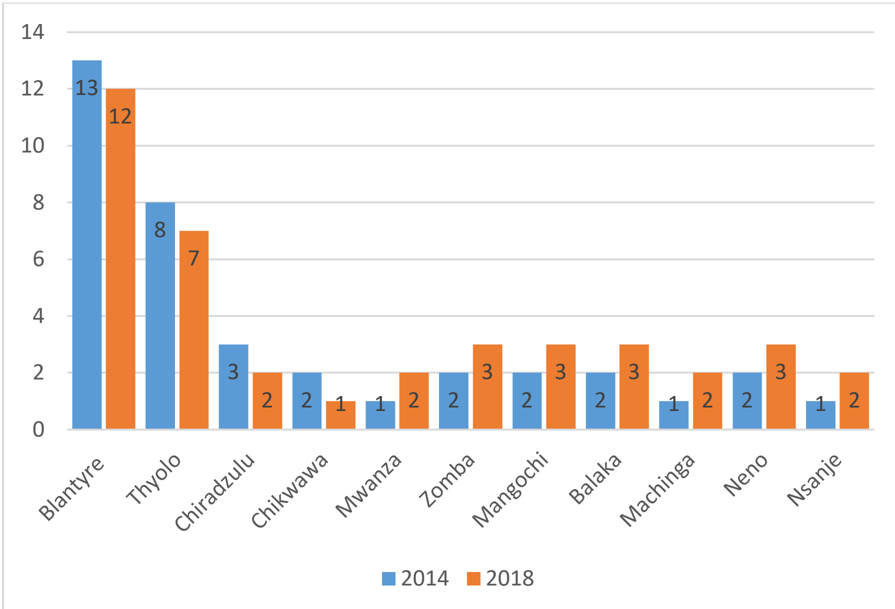

Figure 4: District of origin for cases in 2014 and 2018

There was almost a similar pattern interms of referral of cases in both years. In 2014 a majority of 13 (35%) came from Blantyre district where the referral hospital is located while 3% came from Machinga a district farthest from the referral hospital. The same pattern is seen in 2018 where 12 (30%) came from Blantyre and 2 (5%) from Machinga.

Chapter Five: Discussion

5.1 Prevalence

A 13.8% increase of spina bifida prevalence from 2014 to 2018 might show that the mandatory folic acid fortification programme which was introduced in 2015 had not been effective in reducing the occurrence of spina bifida in that period. The researcher is aware that, the increase could be due to an improvement in referral culture in that period. Literature search and expert consultations did not show initiatives like training and awareness that could lead to the improvement in referral. Furthermore there was no change interms of referral pattern from 2014 to 2018. For example, in 2014, of the 11 districts in the southern region, Mw, a majority of 21 (57 %) came from Blantyre and Thyolo while 1 (3%) came from Machinga. There was a similar trend in 2018 where a majority of 19 (58 %) came from the same districts proximal to the referral hospital and 2 (5%) from Machinga. If there could be some initiave warranting an increase in referral culture, there could be a variation interms of districts of origin from 2014 to 2018. It appears that patients from the districts that were closer to QECH had better chances interms of transport access (both ambulance and private transport), access to information regarding the availability of the services and availability of family support systems during long hospital stays which acted as a motivator for the families to make it to the referral hospital. Blantyre has some health facilities located within a radius of 10 km to QECH, while Machinga was furthest at a distance of 98.3 km.

There was no association between maternal tribe and spina bifida for both 2014 and 2018. Lomwe tribe were in majority for both 2014 and 2018 at 22% and 27.5 % respectively. This should be the case because a majority of Lomwe group comes from districts proximal to the referral hospital i.e Thyolo and Blantyre which produced many cases.

The lower than documented for the region prevalence in the current study could indicate that some patients with spina bifida do not make it to the referral hospital [3]. Various reasons could possibly expain this. For example; pregnancy related losses (still births); a higher than documented mortality in the first days of life before referral is initiated [19, 43]. We singled out birth weight to explain the lower prevalence. In the current study the mean birth weight were 2800g and 2900g for 2014 and 2018 respectively. This is almost similar to the mean birth weight of 2650g obtained by Msamati for Spina bifida in their study at QECH. According to the CDC, newborns should weigh more than 2500g and less than 4 kg [7]. The finding in the study contradicts other studies. For example, in Japan, Kondo (2013) found that babies with low birth weight of less than 2500g were found to be four times more likely to be born with spina bifida than those above [45]. The contradiction in this study could be suggesting that spina bifida babies with lower birth weight were likely not to make to the referral hospital due to death. low birth weight is a significant risk factor for infant mortality [43].

5.2 Gender

Both 2014 and 2018 showed that females were atleast two times more likely to acquire spina bifida than males. This finding agrees with Larry and Paulozzi [16] and Forrester and Merz [11]), who showed that females are more likely than males to have spina bifida [7]. In countries where folic acid fortification programme has been effective, the post fortification period has males more likely to acquire spina bifida than females. This has been the case because folic acid has an increased protective effect on females than males [7]. This means that in countries where folic acid fortification has been effective, the population of male persons with spina bifida becomes more than females due to folic acid averting more female spina bifida cases than males. This revelation affirms that the folic acid fortification programme in Malawi might not have been effective, because had it been that it was effective, we would have seen male gender being associated with spina bifida in 2018.

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5.3 Maternal Age at Delivery

This study has shown that both for 2014 and 2018 a younger maternal age of less than 30 years was significantly associated with giving birth to a child with spina bifida. This agrees with findings of many studies. For example a Malaysian study by Sahmat et al found women at age below 35 years were more likely to give birth to a child with spina bifida [7]. This revelation may imply that even healthy mothers at their ideal childbearing age are also affected and this may be due to genetic or environmental triggers. In the latter case, consumption of fortified folic acid flour would help to reduce the cases of spina bifida [7].

5.4 Family Size

A family size of ≤3 children was associated with a spina bifida prevalence of 76% and 68 % for 2014 and 2018 respectively. This finding is almost similar to Gedefaw who showed that a family size of ≤3 was associated with 73% prevalence of NTD spina bifida inclusive while that of >3, 27% [17]. Possibly this could be the case because in their first children, families might not be oriented to and have no access to pre-conception care that includes folic acid tablet supplementation due to lack of information and experience. This implies that a fortification programme would be more effective if it can place much focus on adolescent girls at risk of bearing children.

5.5 History of Spina Bifida

History of spina bifida was not associated with occurrence of spina bifida.This should justify that the majority of cases of spina bifida are folic acid dependent rather than genetic, giving hope of significant prevention with an effective folic acid fortification programme.

5.6 History of Use of Chronic Medication and Folic Acid Supplementation

It has been shown that a majority of the cases at more than 97% in both 2014 and 2018 neither used chronic medication nor folic acid tablet supplementation. This contradicts an Ethiopian study which revealed that women who used any other drugs other than folic acid or multivitamins were two times more likely to have NTD like spina bifida [4, 17]. In Malawi considering the emergence and increasing number of Non Communicatable Diseases (NCD) it can not be reliable that less than 2 % had used chronic medications in their pregnancy. Possibly mothers could not be comfortable to mention the medication they had been taking due to the stigma attached to them like HAART associated with HIV/AIDS, anticonconvasulats associated with epilepsy. The mothers could not see the importance of mentioning these as they themselves were not the one seeking health care but their children.

The absence of folic acid tablet supplementation in both 2014 and 2018 could be because folic acid is a multivatim that would normally be prescribed as pre-conception care. Since in Malawi, most women might not have started ante natal visits in the first month of pregnancy when the supplementation is uselful, they are likely to miss it [37]. Furhermore, it is not a standard practice in the Malawi context to prescribe folic acid tablet for prevention of Neural Tube Defects like spina bifida. This finding could be showing that an effective fortification programme could help in case reduction.

Chapter Six: Conclusion and Recommendations

6.1 Conclusion

It is shown that the prevalence of spina bifida increased from the pre-fortification to the post-fortification period. A majority of the cases originated from the disricts proximal to the referral facility while a few came from farthest districts to QECH. Spina bifida was significantly associated with gender, negative history of spina bifida, birth weight, family size and maternal age on child bearing. There was no signifance difference in the risk factors in time difference from post-fortificatiom to post-fortification.

6.2 Recomendations

The investigator makes the following recommendations; Firstly, Further research to assess the proportion of spina bifida patients seen at health centers and district hospitals that make it to the referral hospital for treatment. This might help to explain the lower than documented for the region prevalence from the referral hospital.

Secondly, the government should consider constituting a technical team that can include but not limited to nutritionists, food processors, researchers, public health experts and consumer organization whose sole task should be to review an appropriate food vehicle that can reach a majority of the benefiaries with the folate fortificant. Issues of consumer acceptability of the food vehicle to be considered.

Lastly, it is recommended than an additional of non-fortification strategies to the fortification programme be considered. These strategies can include, 1) targeted education programmes for school age girls, 2) free folic acid tablet distribution for girls of child bearing age especially in high risk rural areas (Traditional leaders can pass by-laws to facilitate for this in the villages). The non-fortification strategies become important in Malawian context at the moment because the majority of the population are reliant on milled flour direct from the miller.

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Appendices

Appendix 1: Ethics Approval Certificate

CERTIFICATE OF ETHIC S APPROVAL

This is to certify that the College of Medicine Research and Ethics Committee (COMREC) has reviewed and approved a study entitled:

P.08/19/2780 - Discovering prevalence of spina bifida in southern region of Malawi in order to evaluate the impact of folic acid fortification policy: a central hospital based secondary data study. by Blessings Chapweteka

On 13-Dec-19

As you proceed with the implementation of your study, we would like you to adhere to international ethical guidelines, national guidelines and all requirements by COMREC some of which are indicated on the next page for your study

13-Dec -19

Dr. YB. Mlombe - Chairperson (COMREC)

Date

Approved by
College of Medicine
13-Dec-2019
(COMREC)
Research and Ethics Committee

Appendix 2: Proforma/Data Collection Guidelines

Evaluating the impact of mandatory folic acid fortification program on the prevalence of spina bifida in southern region of Malawi: a central hospital based secondary data study

Study ID____________Date of Data Collection________________**.**

1. Gender of child____. M F
2. Date of birth______________________________.
3. Birth weight____
4. Tribe_____________________________________**1).** Ngoni **2).** Lomwe **3).** Chewa **4).** Sena **5).** Other, specify______________.
5. District of residence____________________________________[Southern region only]
6. Maternal age on delivery_________ **1).** less than 15. **2).**16-20 **3).**21-25 **4).**26-30 **5).** 31-35 **6).** more than 35
7. Number of children by mother________________**1).** 1-2 **2).** 3-4 **3).**5-6 **4).** more than 6
8. Family history of spina Bifida_________________**1).** Yes **2).** No **3).** Not documented
9. History of use of chronic medication ______________**1).** Yes **2).** No
   If yes, specify medication______________.
10. Folic acid use during pregnancy______**1).** Yes **2).** No